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Dermatologic Features of Smith–Magenis Syndrome

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Abstract: **Smith–Magenis syndrome (SMS) is characterized by distinctive facial and skeletal features, developmental delay, cognitive impairment, and behavioral abnormalities, including self-injurious behaviors. We aimed to investigate whether cutaneous features are common in SMS. We performed a complete skin examination in 20 young SMS patients. Skin features secondary to self-injurious behavior, such as bites, abrasions, dystrophic scars, limited spots of hyperkeratosis, anomalies of the nails, and whitlows, were found in the majority of patients. Acral pachydermia and fissured plantar keratoderma were common. Xerosis was constant and associated with extensive keratosis pilaris in the majority of patients. Dermatofibromas were frequent in older patients. The hair was dense and shiny, with an unusual hairline. Eyelash trichomegaly and heavy brows were common, as well as folliculitis on the back. The skin features of SMS have rarely been reported in the literature. Some of these are the consequence of neurobehavioral features, but some cutaneous features and abnormalities of appendages have not been reported in other related syndromes. Skin manifestations of SMS are varied, sometimes induced by self-injurious behavior and sometimes more specific. It remains to be determined whether the combination of the two kinds of signs could contribute to early diagnosis of the syndrome.**

Smith–Magenis syndrome (SMS) is a rare genetic disorder characterized by distinctive facial and skeletal features, developmental delay with low sensitivity to pain and poor reflexes, intellectual disability, sleep disturbances, and self-injurious behaviors. SMS is generally a sporadic disorder caused by a 17p11.2 deletion, encompassing the retinoic-acid-induced 1 *(RAI1)* gene or a mutation of *RAI1*. The incidence of SMS is estimated to be approximately 1 in 25,000 (1–8).

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We saw two young adult patients with SMS in our department: one for psoriasis and one for linear ulcerations of his leg. Both self-perpetuated their lesions by manual aggravation, which led us to address the existence of cutaneous manifestations in SMS.

MATERIALS AND METHODS

Patients with genetically proven SMS were recruited through the patient association ASM 17 France during their annual general meeting. All patients present were included.

Personal interviews were undertaken with children and their parents about subjective dermatologic symptoms such as pruritus and polyembolokoilamania (inserting foreign objects into body orifices), followed by systematic clinical examination of the whole skin and skin appendages.

RESULTS

Dermatologic examination was performed in 20 patients (12 children and 8 young adults, 11 females and 9 males, mean age 13.5 yrs, range 4–30 yrs). All had a 17p11.2 deletion. Twelve patients had pruritus: generalized in eight patients and localized in four patients.

Self-injurious behavior with resulting involvement of the skin or skin appendages was found in 19 patients. Onychotillomania was predominant and was reported for 14 patients who presented with onychophagia (13 patients), nail picking (8 patients), or nail cuticle picking (8 patients). Fingers and toes were affected equally. Self-biting was noted in 12 patients, mostly involving the hands. Three patients had self-inflicted excoriations and burns. Common skin injuries such as bites and abrasions were clearly self-perpetuated in eight patients. Trichotillomania was observed in three children, in one case associated with trichotemnomania (compulsive behavior that consists of cutting one's own hair). Eleven patients had previous or current polyembolokoilamania. In two patients, foreign objects had been introduced under the skin through an open wound.

Skin thickening, or pachydermia, was found in 17 patients. It varied but was always more prominent in distal regions. Fingers were always involved. Joint movement was not restricted, but skin was difficult to pinch. Palms and soles were also involved in 16 and 12 patients, respectively, whereas other areas such as earlobes, limbs, and trunk were sometimes involved, but less significantly (Fig. 1). Mild to moderate plantar keratoderma was found in the same patients, with fissures in 10 patients, on the heel or beneath or between the toes (Fig. 2). Xerosis was found in all patients, predominantly occurring in distal regions; the hands were involved in 18 patients, the feet in 16 patients, the upper limbs in 16 patients, and the lower limbs in 17 patients. Xerosis was diffuse in six patients. Seven children had hyperhidrosis (increased sweating): diffuse in three patients and localized in four patients, involving at least the face in five patients, palms and soles in three patients, and the back in one patient. Dystrophic and pathologic scars were found in 10 patients secondary to skin damage that was traumatic (scratching, biting, cutting) or iatrogenic (chest drainage or laparoscopy) and involved the hands in five patients, upper limbs in five patients, lower limbs in two patients, trunk in two patients, and abdomen, buttocks, or face in one patient each. Limited spots of hyperkeratosis occurred in nine patients and predominated on the hands (seven patients) and on the dorsal side of interphalangeal joints. These skin regions were frequently injured by biting (five patients), sucking (one patient), or both (one patient), sometimes with subsequent calluses (Fig. 3). The other skin areas involved were the knees (five patients) and elbows (one patient). Dermatofibromas were found in four patients, always on the limbs.

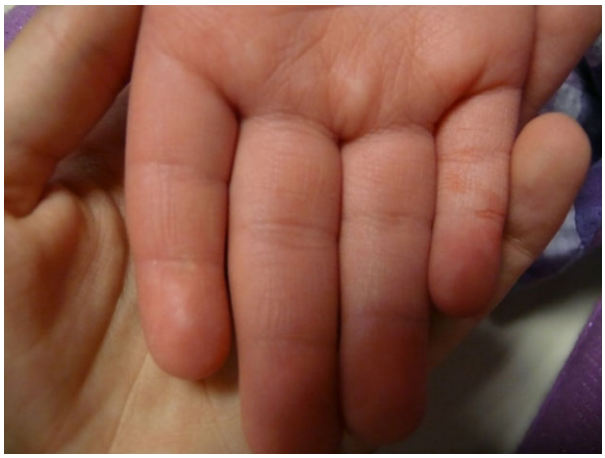

Figure 1. Acral pachydermia in a 6-year-old child.

A receding temple hairline was found in 10 patients. The hair was dense and shiny in 16 patients (Fig. 4). Thirteen patients had keratosis pilaris, mostly on the "usual sites," such as the arms and thighs, but was more extensive, involving the forearms, legs, or buttocks, in four patients. Eleven patients had folliculitis of the middle of the back, varying from sparse lesions on the neck to extensive folliculitis covering the whole back. Eyelash trichomegaly was observed in 13 patients and thick eyebrows with a tendency to synophrys in 10 patients (Figs. 4 and 5). The only anomalies of the nails observed were self-removed nails and short nails as a

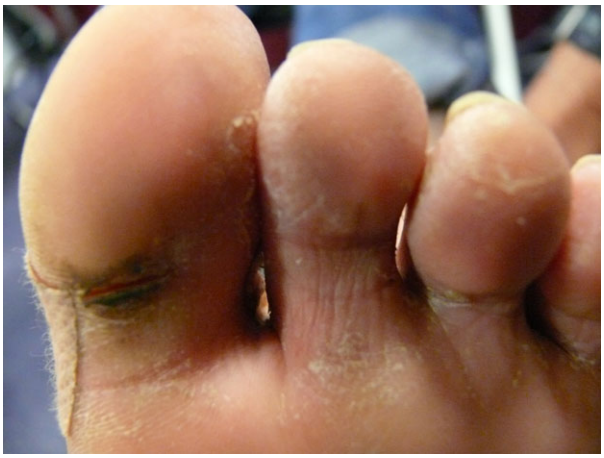

Figure 2. Moderate plantar keratoderma with fissures beneath and between the toes in a 29-year-old woman.

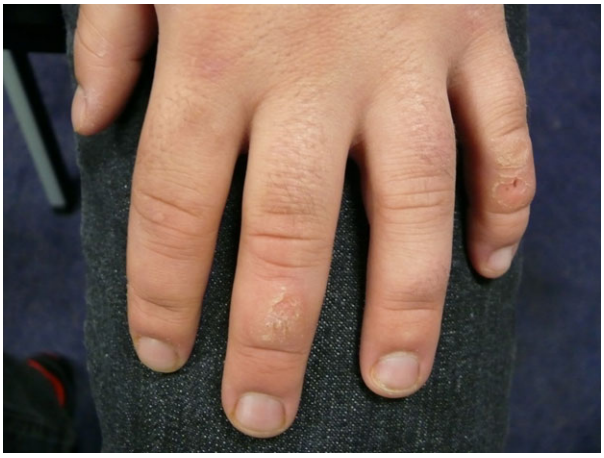

Figure 3. Limited spot of hyperkeratosis on the left hand due to biting in a 21-year-old man.

consequence of onychophagia or onychomadesis due to injury. Eight patients also had perionyxis (paronychia) due to onychotillomania, and five had pachyonychia of one of the toes.

DISCUSSION

This study was conducted in one of the largest cohorts of patients with SMS reported to date. It demonstrated the existence of cutaneous features that were acquired or provoked by self-injury or those presumed to be more specific to the syndrome.

Changes in Skin and Skin Appendages in Relation to Behavioral Abnormalities

Onychotillomania, self-biting, skin picking or burning, and self-perpetuated skin lesions were found in

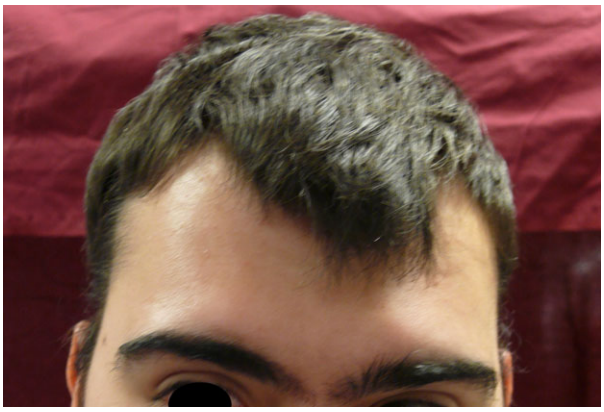

Figure 4. Thick shiny hair with receding temple hairline, thick eyebrows, and synophrys in a 20-year-old man.

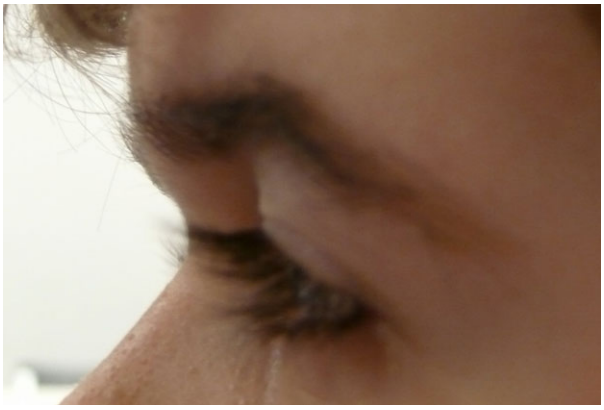

Figure 5. Eyelash trichomegaly in a 9-year-old child.

95% of patients and polyembolokoilamania was found in 55% of patients, which is consistent with previous publications (2,3,5). A minority of these patients also had trichotillomania, and one had trichotemnomania, which has rarely been reported. Some dermatologic features highlighted in our cohort seemed to be totally or partially linked to these behavioral features.

Whitlows represented the most common dermatologic history reported. Finger licking and onychotillomania probably partly accounted for the occurrence of whitlows and contributed to delayed healing. Half of the patients who had a history of whitlows tended to self-perpetuate their skin lesions. Thick spots of hyperkeratosis and callus formation often occurred on sites resulting from regular self-injurious behavior. Scars were secondary to traumatic injuries or occurred after surgical incisions.

Few dermatologic features have been reported in association with other genetic disorders sharing a few phenotypic features of SMS, particularly self-inflicted injury. Prevalence rates could not be found in the

literature. Most of the time there is no obvious association between the self-injurious behavior and the dermatologic features reported. Skin picking observed in Prader–Willi syndrome has been correlated with recurring infections and has been associated with trichotillomania, onychophagia, edema of the lower limbs, and hypopigmentation (9–11). Only synophrys and eyelash trichomegaly have been described in Cornelia de Lange syndrome (12). Patients with Kleefstra syndrome (9q34 deletion) have occasionally presented with synophrys or arched eyebrows, alopecia, and depigmented skin patches (13). The main dermatologic features reported in Down syndrome (soft, velvety skin in childhood, then xerosis, ichthyosis vulgaris, keratosis pilaris, palmoplantar keratoderma, fine sparse hair, short eyebrows) seem not to be related to behavioral abnormalities. Patchy lichenification and calluses have been observed over friction areas, without obvious association with (self-)injury (14,15). Hypopigmentation of skin and hair and sparse frontotemporal hair have been observed in Angelman syndrome (16). In Prader–Willi syndrome and Down syndrome, as in SMS, there is a lack of sensitivity that probably explains the occurrence of trauma and secondary skin lesions.

Potocki–Lupski syndrome, or duplication 17p11.2 syndrome, is the reciprocal microduplication syndrome of SMS. No cutaneous features have been reported in this syndrome (17).

Changes in Skin and Skin Appendages That Have Not Been Found in Other Similar Syndromes

Xerosis is known to be associated with SMS in patients with an *RAI1* mutation (6). It probably contributes to pruritus. Pruritus could also be the starting point for skin damage that is subsequently self-perpetuated. Keratosis pilaris, known to be possibly pruritic, was found in the vast majority of patients, predominantly in the adults. It was not atrophic, in contrast to keratosis pilaris associated with certain other genetic diseases (18).

Pachydermia, dystrophic scars, dermatofibromas, hairline abnormality, and thickness and shininess of the hair have not been found in other genetic diseases and appear more specific to SMS. Pachydermia was found in the majority of our patients. It can cause traumatic lesions through a mechanical effect and is probably an important factor in healing difficulties, as the presence of dystrophic scars indicates. Dermatofibromas were frequent in the older patients in our SMS cohort, and appeared more frequently and earlier than in the general population of the same age. Hair and eyebrows in SMS patients were particularly thick and shiny and were often associated with eyelash trichomegaly, which has not been described before (1,2,4). Folliculitis in the middle of the back was unlikely to be linked to behavioral abnormalities because it occurred in areas inaccessible to scratching. Its origin is unclear, but is possibly linked to friction, occlusion, soaked skin, or excessive weight. Pachyonychia of the toes was found in five patients. Its origin might be mechanical, because of repeated trauma, or linked to inappropriate footwear in the context of foot deformities (1,2,4). These non-self-inflicted cutaneous features might help differentiate SMS from the other disorders that are characterized by self-inflicted injury.

An understanding of the skin features in SMS might assist in earlier detection of the syndrome, especially when neurologic and behavioral features have not become specific and may evoke other syndromes. Certain clinical cutaneous features such as acral pachydermia, particular hairline abnormalities, heavy brows, and eyelash trichomegaly appear early and could suggest the diagnosis, especially if they are associated with self-injurious behavior. The cutaneous phenotype probably worsens with age since the prevalence of pachydermia, dermatofibromas, xerosis, plantar keratoderma, keratosis pilaris, median folliculitis of the back, and dense and shiny hair is greater in older patients. This progression with age has already been described for other features associated with SMS (2). A similar study in an older SMS population would therefore be interesting.

From a therapeutic point of view, moisturizers might help to decrease skin dryness and prevent pruritus and hence the risk of injury, but this remains to be evaluated. Occlusive dressings can prevent self-perpetuated lesions.

CONCLUSION

Some of the skin findings in this study were secondary to the behavioral features of the patients and can be found in other conditions with comparable behavior. The other clinical cutaneous and skin appendage features observed in the majority of patients were xerosis, acral pachydermia with disordered healing, plantar keratoderma, thick shiny hair with particular implantation features, median folliculitis of the back, eyelash trichomegaly, and thick eyebrows and appeared to be more specific to SMS. It remains to be determined whether a combination of the two kinds of signs could assist in early diagnosis of the syndrome.

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