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SJÖGREN-LARSSON SYNDROME: MICROSCOPIC AND SCANNING ELECTRON MICROSCOPIC FINDINGS IN REPLICAS OF THE SKIN

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Abstract. Replicas of the skin below the cubital fossa were made in 29 SLS patients with an age range of 8 days to 69 years. The skin surface patterns differed from those in healthy controls. The papillomatosis observed in most SLS replicas seemed to appear during the first year or years of life and to increase in some patients with increasing age, but seemed to diminish again in middle-aged and older SLS patients. Other common features were the occurrence of longitudinal and transverse furrows. All these findings in SLS patients could, at least in part, represent an exaggeration of the normal skin surface pattern. The use of replicas for diagnostic purposes is commented on.

Key words: Sjögren-Larsson syndrome; Ichthyosis; Skin surface replicas; Scanning electron microscopy

The Sjögren-Larsson syndrome (SLS) is an autosomally recessively inherited disorder characterized by three cardinal signs, congenital ichthyosis, spastic di/tetraplegia, and mental retardation (1, 3, 4, 8, 11). In SLS patients exceeding one year of age there is also seemingly a fourth cardinal sign—glistening dots in the ocular fundi (5). The histopathological findings in cutaneous biopsy specimens have recently been described (2). Amongst other things, papillomatosis was observed. This type of finding will probably be better defined by studying the surface than by examining histological sections, where chance may decide whether the sections come through the middle part of the papillae or in the furrow in between them. The replica technique (6, 9) has previously been used in the study of ichthyoses (7), and this technique was found suitable for use in the present investigation.

The aim of this study was (1) to find out the typical characteristics of the skin surface in SLS (2) to examine the possibility of age-related differences, and (3) to compare the findings with those in healthy individuals and patients with other types of ichthyosis.

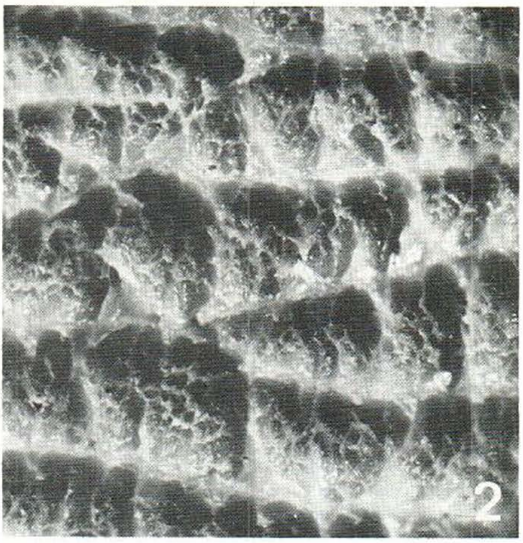
MATERIAL AND METHODS

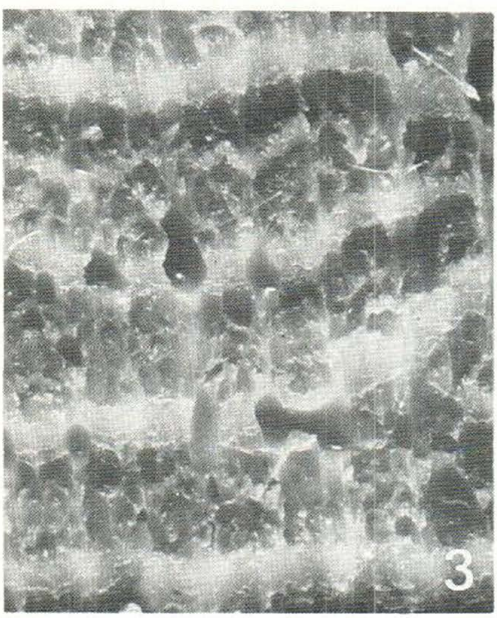
In connection with a systematic clinical study of all 35 SLS patients alive in Sweden in 1978 and one more born in 1980, replicas were made from the same area as the skin biopsy specimens were taken. Thus replicas with a diameter of at least 2 cm were made from the volar aspect of the right forearm 2–4 cm distal to the cubital fossa in 29 of the 36 SLS patients, in a few patients with other types of ichthyosis included in the search for SLS individuals (for details, see cases 1–9, 15–27, 29–31, 34, 35, 40–43, 45–52 in Table 1 in Hofer & Jagell, 1981) and in 7 healthy controls numbered cases 53–59 (age 7 days, one, 2, 5, 14, 30, and 69 years respectively). From patients with SLS, occasional replicas were also made from other cutaneous regions.

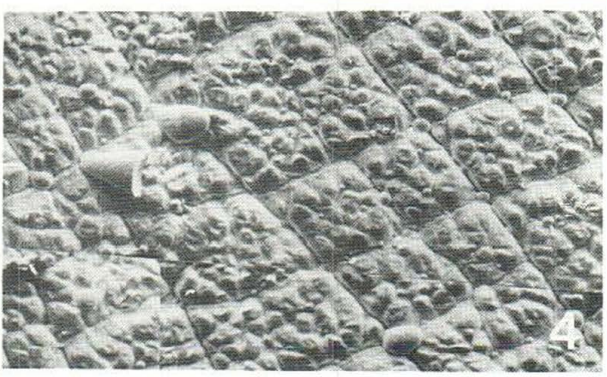
In a few SLS patients one replica was made with the arm extended and another with the elbow bent at a right angle. Concerning the technique, a primary replica of the skin was made *ad modum* Sarkany (1962) using a silicone rubber monomer. This replica was studied in a dissection microscope at low magnification in order to permit comparison with reported findings in other types of ichthyosis (7), and in some cases low-power microphotographs were taken. From the primary replica, in 10 cases a secondary replica was made as described by Johnson et al. (1970), but using Epon instead of Araldite. This Epon replica was coated with a thin layer of gold in a vacuum evaporator and examined in a Cambridge Stereoscan Microscope S 4. Such a secondary replica not only has a surface corresponding to the original skin surface, but is also photographically preferable if the surface is not relatively flat, owing to the larger depths of focus in the scanning electron microscope compared with close-ups with the light-microscopic technique with its small focal depths.

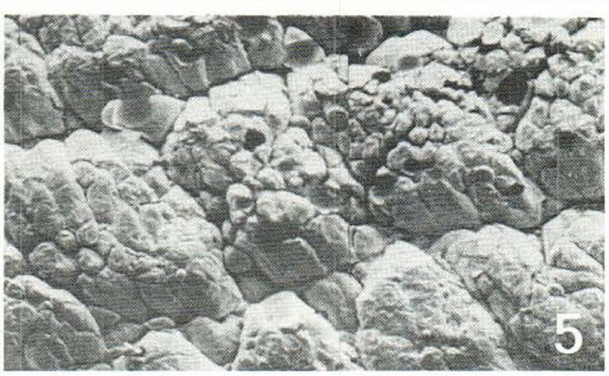
RESULTS

Although mainly primary replicas were examined, representing mirror images of the skin surface, the following descriptions concern the corresponding appearance of the skin surface. In the youngest SLS patient (case 52), thin, shallow, closely located longitudinal furrows were seen. This finding did not differ from that in a patient (case 51) of the same age but with a recessively inherited ichthyosis congeni-









Figs. 1–3. Silicon rubber replica series of the skin surface just below the right cubital fossa. *1.* Female, 2-year-old SLS patient. Shallow furrows in the skin form a square pattern of low ridges in the replica. Impressions of blunt and short papillae are also seen (×9). *2.* Male, 16-year-old SLS patient with a characteristic pattern, where the transverse furrows form ridges in the replica. In between these ridges, impressions of papillae are seen. The light microscopic technique does not give at true picture of the depth of these impressions (×9). *3.* Male, 19-year-old patient. Unusually marked longitudinal furrows form ridges in the replica (vertical in photograph). It is difficult to identify impressions of papillae in such a marked pattern of furrows (ridges in replica) when light microscopic technique is used (×10).

Figs. 4 and 5. Scanning electron micrographs of the secondary replica of primary replica illustrated in Figs. 1 and 2, respectively. *4.* Note square pattern of shallow furrows and blunt papillae (×12). *5.* Transverse deep and broad furrows with interposed long papillae are seen (×14).

ta of a non-SLS type. Longitudinal furrows were also observed in the other SLS patients (Figs. 1–5), with a different appearance in different patients. They could be deep or shallow and close to or more distant from each other. They were absent only in the oldest patient (case 7). Transverse furrows occurred in all patients except the youngest one (case 52). Their depth differed in different patients. Both longitudinal and transverse furrows were only slightly pronounced in the 2 youngest patients with papillomatosis (cases 4 and 26), making the skin surface relatively flat, with the furrows forming squares (Figs. 2, 4). Otherwise, in most of the SLS patients the transverse furrows predominated, being broader and deeper than the longitudinal ones (Figs. 3, 5). In the oldest patients the findings are better described as transverse ridges.

Papillomatosis of differing degrees i different patients was seen in all SLS patients (table of degree of papillomatosis in individual SLS patients is available from the authors) except the youngest one (case 52). In SLS patients aged 1–2 years the papillomatosis was slight. The group of SLS patients 3–28 years old displayed a papillomatosis varying from slight to pronounced in degree. In the older SLS patients the papillomatosis was again only slight.

When the elbow was stretched the replica pattern was less pronounced than when the elbow was bent, but the differences were small. The few replicas representing a preliminary study of other locations added little to the knowledge about the skin surface in SLS, except that replicas from the neck could resemble those from the area below the cubital fossa. In healthy controls, short, shallow, densely located furrows formed a pattern consisting of small fields, often triangular. Some longitudinal and transverse furrows, particularly longitudinal furrows in the youngest healthy controls, could be slightly more marked, but never so marked as was usual in SLS skin. Particularly the transverse furrows were deeper, broader and more sparsely located in SLS. The SLS papillae could perhaps represent an exaggeration of the normally occurring pattern of small fields surrounded by small furrows. Patients with ichthyosis vulgaris and X-linked ichthyosis differed from healthy controls by having slightly more pronounced coarse furrows, whereas finer furrows were less evident, or lacking. Thus, the skin surface did not resemble that in SLS.

Two patients originally reported by Sjögren & Larsson (1957) as having SLS but later found not to have this syndrome (1, 4), a woman (case 6) and her brother (case 18), with ichthyosis and mental retardation but without spasticity, were also included in the examination. Their replicas had a pattern quite different from that in SLS, characterized by large, sharp-edged scales. In 2 cases the replicas of other types of ichthyosis did not differ from those of the SLS type. Both the replica from a young SLS patient (case 52) and that from a patient of corresponding age with recessively inherited ichthyosis congenita lacked papillomatosis. However, the non-SLS child was free from skin lesions at a re-examination at 11 months of age. The findings in the skin replica from a patient with 'Rud's syndrome' were of the same nature as in SLS replicas.

DISCUSSION

Concerning the examined area below the cubital fossa, an analysis of three components of the replicas, namely longitudinal furrows, transverse furrows, and papillomatosis, indicates the following development of the cutaneous surface. Longitudinal furrows are the only characteristic in the newborn SLS patient. During the first years of life the pattern changes, so that shallow transverse and longitudinal furrows form squares whose surfaces are covered with short, blunt papillae. Later on, the furrows often become more marked, usually with a predominance of transverse ones. In older children, adolescents and young adults with SLS the papillomatosis often becomes more pronounced, whereas in older patients it is again only slight.

No close correlation was found between the degree of papillomatosis in replicas and that in biopsy specimens from the same area. One possible explanation is that the papillomatosis only occurs in between the furrows, which would mean that chance would decide whether and to what extent the papillomatosis can be observed in the sections. On the other hand, the possibility cannot be excluded that the degree of hyperkeratosis may influence the degree to which papillomatosis is seen on the replicas. In the series of replicas of ichthyotic skin reported by Kuokkanen (1972), there were usually no similarities to our findings in SLS. Our observations also indicate a lack of similarity between SLS, and two other types of ichthyosis, namely ichthyosis vulgaris and X-linked ichthyosis. In a patient with dominantly inherited congenital ichthyosis reported

by Kuokkanen (1972), however, a skin replica from the wrist showed a pattern resembling our finding in SLS skin below the cubital fossa.

Recessively inherited ichtyosis was not represented in Kuokkanen's report (1972). In our study, a woman and her brother with another type of recessively inherited ichthyosis showed histopathological skin findings that could not be differentiated with certainty from SLS (2) but their replicas were quite different from those in SLS. On the other hand, a replica from the elbow in a patient with 'Rud's syndrome' did not differ in appearance from those in SLS. It is of course possible that other regions in Rud's syndrome may have a skin surface pattern divergent from that in SLS. In any case the skin biopsy specimen from this patient (biopsy location not noted) showed relatively pronounced parakeratosis, of a degree usually not seen in SLS biopsy specimens.

The characteristic skin findings observed in the present study indicate that the use of replicas in ichthyotic patients may be a good complement to the clinical and histopathological examinations.

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